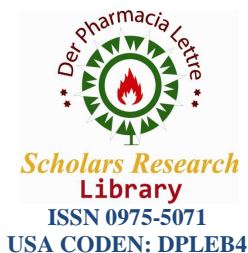




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Formulation and evaluation of oro-dispersible tablets of lafutidine

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ABSTRACT

The purpose of present investigation was used to develop and evaluate orodispersible tablets of lafutidine, because it is used in patients recurrently suffered from peptic ulcer, and it is used as a pre-anaesthetic medication, fast onset of action and avoidance of water is highly desirable. Tablets were prepared by direct compression by using three superdisintegrants of sodium starch glycolate, crospovidone and Croscarmellose Sodium were used alone as well as in combination. The combination of superdisintegrants gave better disintegration effect. Micro crystalline cellulose was used as diluent, mannitol and aspartame were used to enhance the organoleptic properties of tablets. The dissolution studies were conducted in 900 ml of pH 6.8 phosphate buffer. The optimized formulation F-12 showed good release profile with maximum drug release at all time intervals. The drugs with other excipients were interaction evaluated by FTIR. FTIR spectrum of pure drug was compared with other formulations. All peaks corresponding to the different functional groups of the pure drug were present in the formulations which indicate the absence of interaction between the drug and excipients. The selected formulation F-12 was subjected for stability studies as per ICH guidelines. Formulations subjected for stability studies were checked for drug content, hardness, friability and physical appearance for 90 days with an interval of 15 days. The formulations were found to be stable as no significant change was observed in the various evaluated parameters of the formulations. It was concluded that orodispersible tablets of Lafutidine could be prepared by using blend of all three superdisintegrants. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Keywords: Orodispersible tablet, Crospovidine, Crosscarmellose sodium, Sodium starch glycolate, FTIR - Fourier Transform infrared spectroscopy.

INTRODUCTION

The demand for developing new technologies has been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency and the production of more cost effective dosage forms. For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration, owing to its several advantages and high patient compliance compared to many other routes. However, many patient groups such as the elderly, children and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Those who are traveling or have little access to water are similarly affected.

To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as Orally Disintegrating Tablets which disintegrate rapidly in saliva without the need to take it with water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability maybe significantly greater than those observed from conventional dosage forms¹.

Lafutidine effectively inhibits gastric acid secretion during the day time not only by blocking H₂-receptor but also through histamine-independent indirect action, raising the possible contribution of this agent to the treatment of patients with acid-related diseases².

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8% with the optimum concentration about 4% although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling³.

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet granulation and dry granulation methods⁴.

Crosscarmellose sodium as a disintegrant for tablets (wet granulation and direct compression), capsules and granules at a concentration of 2 - 5%⁵.

The aim of the present work was to formulate and to evaluate the orodispersible tablets of anti ulcer drug by direct compression method using blend of superdisintegrants

MATERIALS AND METHODS

Lafutidine was obtained as a gift sample from G.K.M new pharma,puducherry , sodium starch glycolate and aspartame purchased from Hi media Lab pvt Limited , crospovidone and crosscarmellose sodium purchased from Research- Lab Fine Chem industries, , lactose, talc ,magnesium stearate lubricant, mannitol, aspartame and micro crystalline cellulose purchased from S D Fine Chem .Limited.

Compatibility studies (Fourier Transform Infrared Spectroscopic studies) Procedure:

To study the compatibility of various formulation excipients with lafutidine, solid admixtures were prepared by mixing the drug with each formulation excipient separately and stored in air tight containers at 30 ±2/65±5%RH. The solid admixtures were characterized using fourier transform infrared spectroscopy (FT-IR).

PREPARATION OF ORODISPERSIBLE LAFUTIDINE TABLETS :

Lafutidine is mixed with super disintegrate Crospovidone, Sodium starch glycolate, Crosscarmellose Sodium, Mannitol mouth feel enhancer, Microcrystalline cellulose as diluted and binder, lactose as diluent, aspartame as sweetner, talc as glidant and magnesium stearate as lubricant. All the ingredients were passed through #60 mesh separately, weighed and mixed in geometrical order in to motor and pestle for 10 min. The blend thus obtained was directly compressed on 10 station rotary punching machine to get 10 mg of lafutidine, each tablets weighing of 200 mg.

F1, F2, F3 Formulation are prepared by using sodium starch glycolate superdisintegrant in 2%, 3%, 4% respectively. F4, F5, F6 Formulation prepared by using crospovidone superdisintegrant in 2%, 3%, 4% respectively. F7, F8 , F9 Formulation prepared by using crosscarmellose sodium superdisintegrants in 2%,3%,4% Respectively.⁶

F10,F11,F12 Formulation prepared by using Combination of Sodium starch glycolate , crospovidone , crosscarmellose sodium in 3% ,4.5%, 12% respectively.⁷

COMPOSITION OF ORODISPERSIBLE TABLET OF LAFUTIDINE :

Table 1: Composition of (F1to F12)formulation

INGREDIENTS(mg)	GROUP A			GROUP B			GROUP C			GROUP D		
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Lafutidine	10	10	10	10	10	10	10	10	10	10	10	10
Sodium starch glycolate	4	6	8	-	-	-	-	-	-	-	-	-
Crosspovidone	-	-	-	4	6	8	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	-	-	-	4	6	8	-	-	-
Sodium starch glycolate+ Crosspovidone+ Croscarmellose sodium	-	-	-	-	-	-	-	-	-	6	9	12
Microcrystalline cellulose	90	90	90	90	90	90	90	90	90	90	90	90
Lactose	54	52	50	54	52	50	54	52	50	52	49	46
Mannitol	20	20	20	20	20	20	20	20	20	20	20	20
Aspartame	10	10	10	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2

IN-VITRO DRUG RELEASE STUDIES:

In-vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of pH 7.4 phosphate buffer, maintained at 37±0.5°C. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Labindia, Mumbai, India) at 226 nm. The study was performed in triplicate.

RESULTS AND DISCUSSION

Orodispersible tablets have proven popular because of the simplicity of the manufacturing processes required, level of reproducibility, stability of the raw materials and dosage form as well as ease of scale up operation, validation and favorable *in-vitro*, *in-vivo* correlation. Three superdisintegrating agents are used at lower, medium & higher concentration twelve formulations were designed. All the Superdisintegrants such as crospovidone, sodium starch glycolate, croscarmellose sodium were added in different concentration and blend of all superdisintegrants crospovidone, sodium starch glycolate, croscarmellose sodium, Mannitol were used as diluent, talc was used as glidant, magnesium stearate used as lubricant, aspartame used as a sweeteners. Each formulation was composed of drug and excipients in various preparations. This design technique was used to optimize and obtain a better formulation with respect to *in-vitro* dispersion time, wetting time and water absorption ratio. Incompatibility studies of FTIR confirmed that there is no interaction between drug and excipients used in the formulations. Compatibility of the drug with excipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after mixing it with the excipients. All FTIR graphs shown in figure no 1-8

The bulk density of the powdered blend was found to be 0.680 - 0.711 gm/cm³, tapped density between 0.775 - 0.875 gm/cm³ for all formulations. % Compressibility, Hausner ratio was found to be between IP limit (table no. 14). Drug content was found to be 98-99.3 % (table no. 17) Angle of Repose was found in the range of 21.97° ± 0.09 to 29.40° ± 0.41. Friability (%) was found to be below 1%. Hardness was found to be 4.1 - 4.8 kg/cm² (table no. 15) Dissolution profiles of all the batch were found to be in the range 75-98.5 %, the results are shown in the table no. 20 The flow properties of the powdered blend for all the batches were found to be good and free flowing. The hardness and friability of all the formulated tablets within the specified requirements. The disintegration times for the formulated tablets are within (180secs) the range of European Pharmacopoeia. Weight variation test helps to check whether the tablet contain proper quantity of the drug. From each of the formulations twenty tablets were randomly selected and weighed. The results are given in table (2-5). The average weights of the tablets were found to be within the prescribed official limits (IP). Drug content for each of the formulations were estimated. The drug content for all the batches were found to be in the range of 98.20 to 99.30%. Here *in-vitro* drug release show that formula have crospovidone, sodium starch glycolate, croscarmellose sodium, which have more disintegration time as compare to the blend of all superdisintegrants less disintegration time than others. The faster disintegration of blend of all superdisintegrants tablets may attributed to its rapid capillary activity and pronounced hydration with little tendency to gel formation. Thus, these results can suggest that the disintegration times can be decreased by using wicking type of disintegrants crospovidone, sodium starch glycolate, croscarmellose sodium, used alone. So batch no. F12 blend all superdisintegrants(6%) is best due to less disintegration time and high water absorption ratio.

Drug and disintegrants interactions were checked by comparing the IR spectra of the formulations with the IR spectra of the pure drug. There was no significant change in the functional groups between the IR spectrum of the pure drug and also no additional peaks were seen in the selected formulations (figures 1-8). This confirms that no interaction between drug-excipients and also final optimized formulation. Stability studies were carried out on F-12 formulation as per ICH guidelines. There was no much variation in matrix integrity of the tablets at all the temperature conditions. There was no significant changes in drug content, physical stability, hardness, friability and drug release (tables 2-5) for the selected formulation F-12 after 90 days at $250\text{C} \pm 2^{\circ}\text{C} / 60\% \pm 5\% \text{RH}$, $30^{\circ}\text{C} \pm 2^{\circ}\text{C} / 65\% \pm 5\% \text{RH}$ and $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5\% \text{RH}$.

CONCLUSION

Orodispersible tablet is a promising approach with a view of obtaining faster action of drug and would be advantageous in comparison to currently available conventional forms. In this study orodispersible tablets of lafutidine were prepared by direct compression method using crospovidone, croscarmellose sodium and sodium starch glycolate superdisintegrants and blend of all superdisintegrants. Superdisintegrants are used that swell or absorb water rapidly to disintegrate the tablet. These agents bring about fast disintegration due to increased water uptake which causes explosion of tablet matrix which leads to decrease disintegration time. The formulation F12 containing crospovidone, sodium starch glycolate, croscarmellose sodium, respectively showed faster disintegration. Different parameters like hardness, friability, weight variation, drug content uniformity, *in-vitro* drug release etc. were evaluated for these formulations. The optimized formulation F12 showed good release profile with maximum drug being released at all time intervals. It was concluded that orodispersible tablets of lafutidine could be prepared by using blend of superdisintegrants by direct compression method. The release of drug from the F-12 formulation was quick when compared to other formulations. Based on these results formulations F-12 was found to be the most promising formulation. In an *in vitro* model, the sodium bicarbonate buffer rapidly increases the pH to greater than 6 within one minute and sustains this pH environment for approximately 30 minutes. Stability study was conducted for the optimized formulation as per ICH guidelines for a period of 90 days which revealed the stability of the formulation. The results suggest that the developed orodispersible tablets of lafutidine could perform better than conventional dosage forms. Thus the aim of this study was achieved.

DRUG – EXCIPIENTS COMPATIBILITY STUDIES:

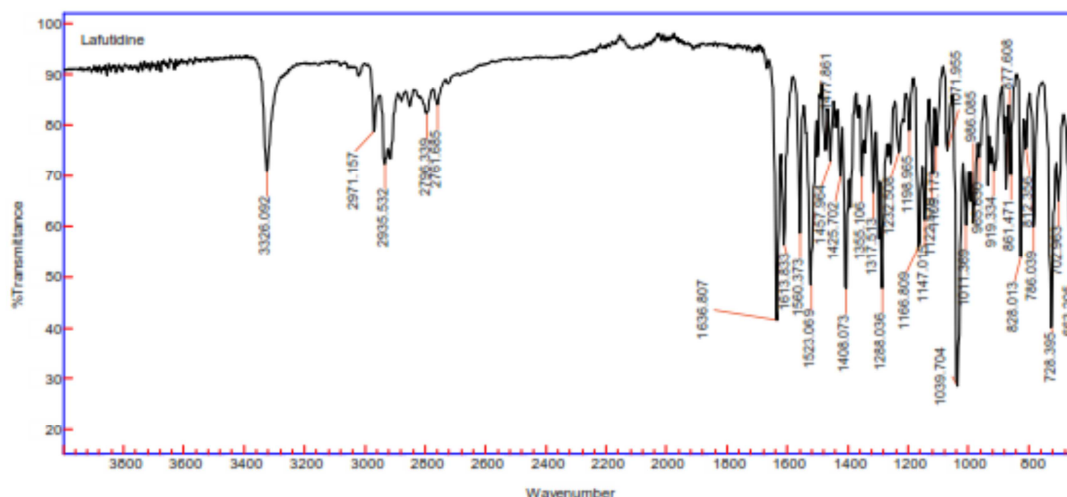


Figure 1 : FTIR spectrum of pure drug lafutidine

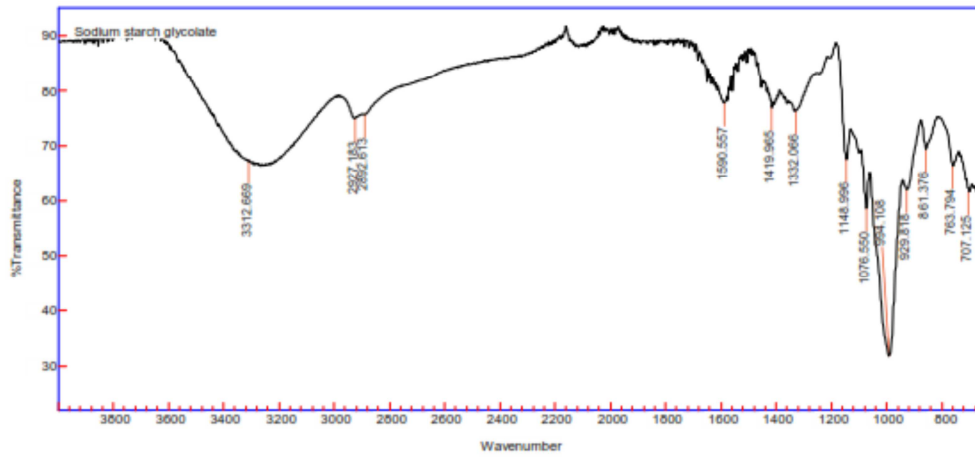


Figure 2: FTIR spectrum of Sodium Starch Glycolate

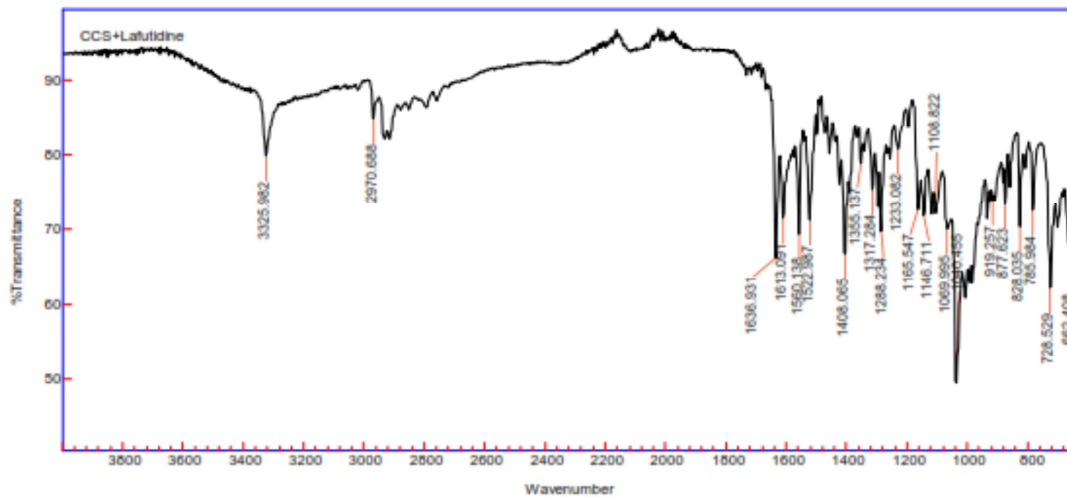


Figure 3: FTIR Spectrum of Crospovidone

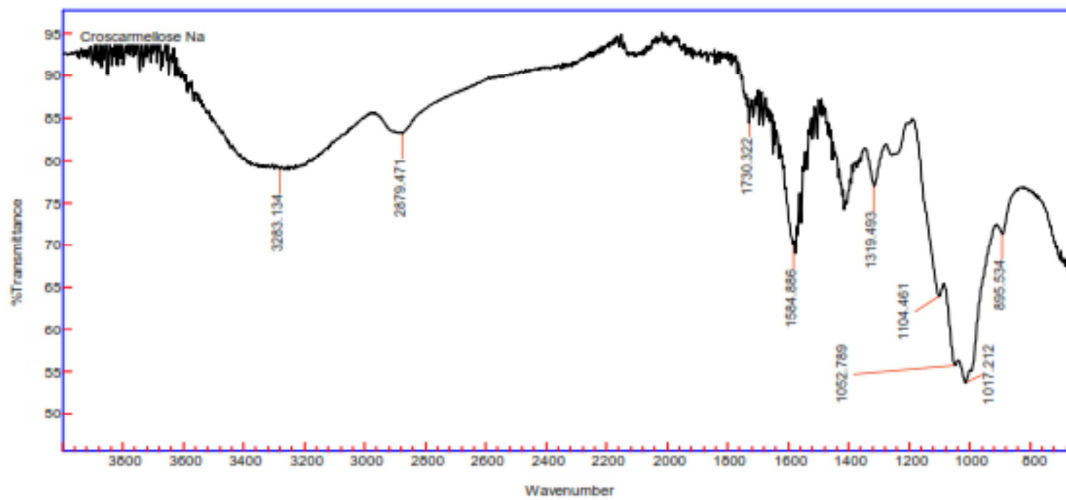


Figure 4 : FTIR Spectrum of Croscarmellose Sodium

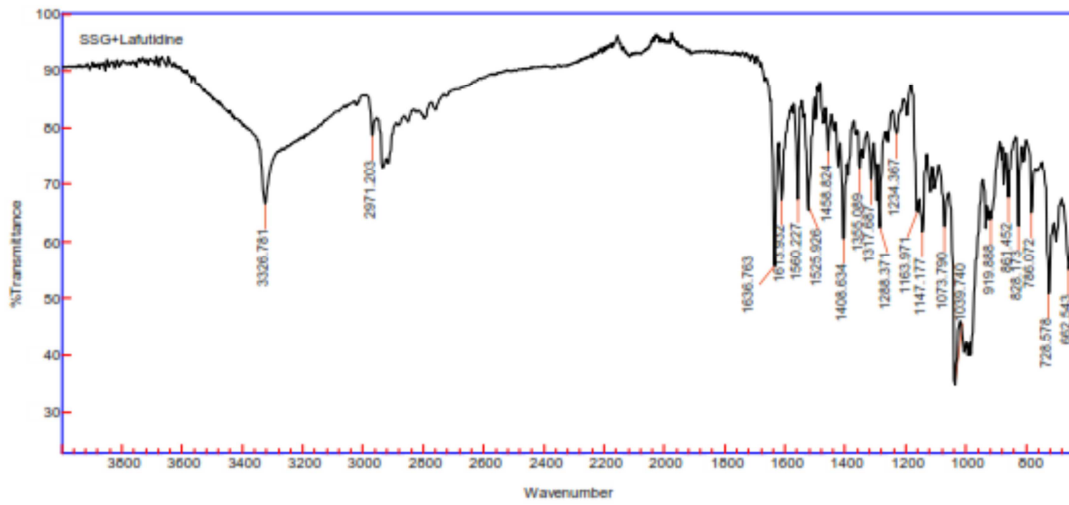


Figure 5 : FTIR Spectrum of sodium starch glycolate + Lafutidine

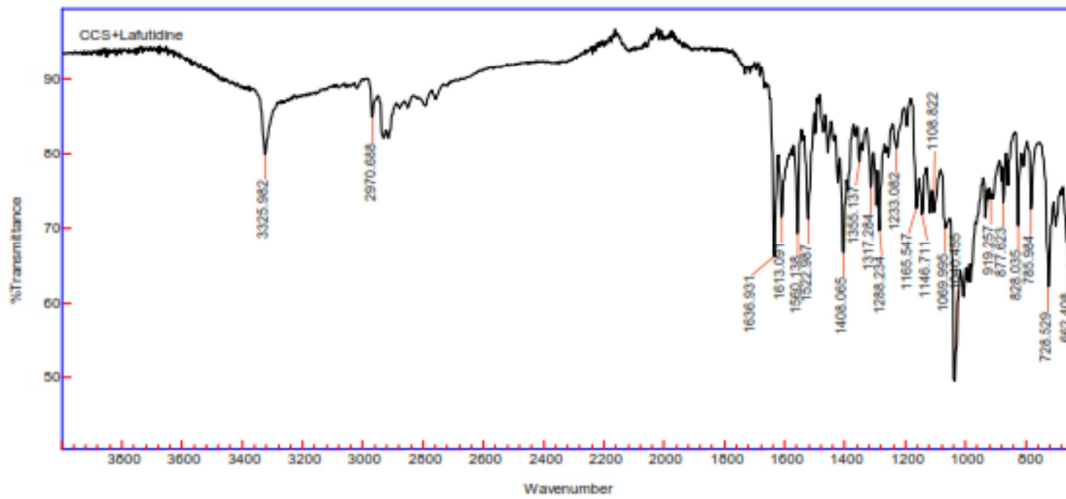


Figure 6 : FTIR Spectrum of croscamellose sodium +lafutidine

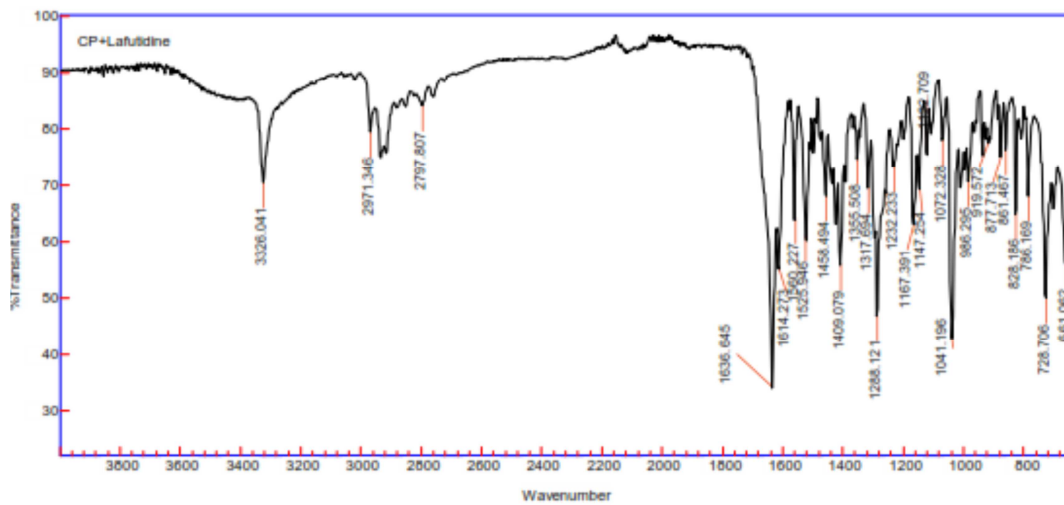


Figure 7 : FTIR Spectrum of Crospovidone +Lafutidine

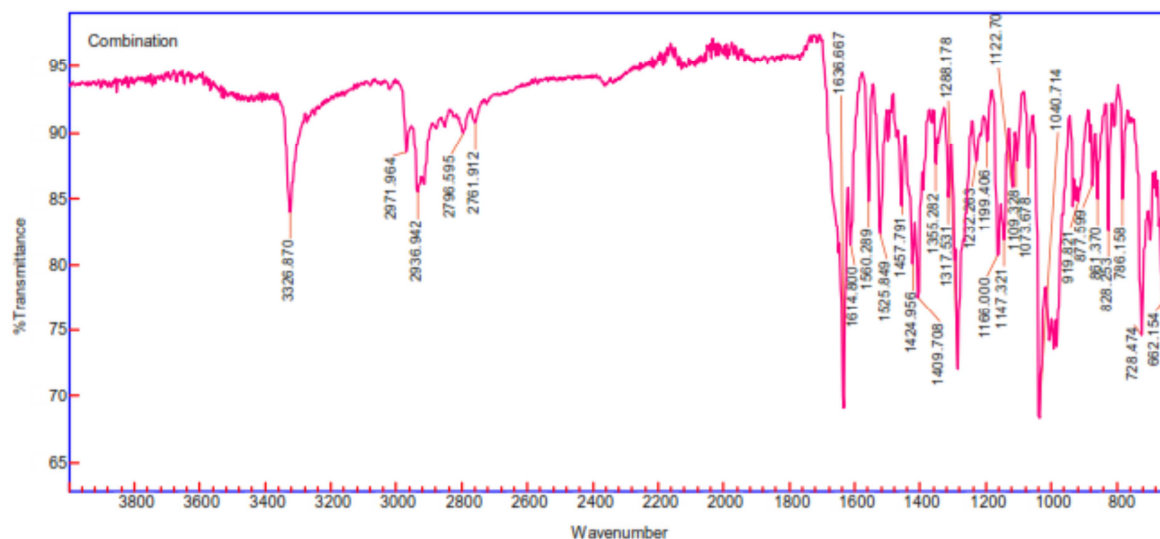


Figure 8 :FTIR Spectrum of Sodium Starch Glycolate + Crospovidone +Lafutidine+ Croscamellose Sodium

PRE COMPRESSION PARAMETER:

Table 2: Data for blend evaluation of formulation (F-1 to F-12)

FORMULATION CODE	Parameters				
	Angle of repose (°)	Loose bulk density (LBD) (g/ml)	Tapped bulk density (TBD) (g/ml)	Compressibility index (%)	Hausner Ratio
F-1	21.97± 0.09	0.704±0.07	0.775±0.19	09.16	1.10
F-2	28.12± 0.12	0.684±0.18	0.833±0.31	17.89	1.21
F-3	27.34± 0.29	0.693±0.65	0.806±0.23	13.97	1.16
F-4	28.61± 0.10	0.687±0.35	0.840±0.24	18.17	1.22
F-5	24.05± 0.39	0.707±0.17	0.848±0.09	16.66	1.20
F-6	24.51± 0.19	0.685±0.20	0.824±0.28	16.86	1.20
F-7	27.37± 0.24	0.711±0.12	0.790±0.19	10.00	1.11
F-8	29.40± 0.41	0.70±0.16	0.875±0.41	20.00	1.25
F-9	25.75± 0.12	0.697±0.35	0.776±0.29	10.23	1.11
F-10	29.40± 0.41	0.70±0.16	0.875±0.41	20.00	1.25
F-11	28.61± 0.10	0.687±0.35	0.840±0.24	18.17	1.22
F-12	27.34± 0.29	0.693±0.65	0.806±0.23	13.97	1.16

POST COMPRESSION PARAMETERS :

Table 3: Physical properties and % drug content (F-1 to F-12)

FORMULATION CODE	Parameters			% of drug content
	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	
F-1	4.16± 0.09	4.5±1.3	0.485	98.2
F-2	4.12± 0.02	4.2±1.8	0.441	98.9
F-3	4.11± 0.10	4.2±2.0	0.551	99.1
F-4	4.10± 0.09	4.1±1.1	0.539	99.0
F-5	4.05± 0.03	4.3±1.7	0.459	98.7
F-6	4.11± 0.07	4.8±1.3	0.468	98.5
F-7	4.05± 0.02	4.5±1.2	0.578	99.3
F-8	4.07± 0.08	4.2±1.3	0.590	98.8
F-9	4.04± 0.06	4.6±1.6	0.521	98.2
F-10	4.07± 0.08	4.2±1.3	0.590	99.1
F-11	4.10± 0.09	4.1±1.1	0.539	98.7
F-12	4.11± 0.10	4.2±2.0	0.551	99.5

WETTING TIME:**Table 4: Wetting time in second for formulations F-1 to F-12**

Tablet formulation	Wetting time in sec.	Water absorption ratio (%)
F-1	49	75.18
F-2	52	71.28
F-3	45	75.18
F-4	52	60.58
F-5	50	78.83
F-6	65	64.23
F-7	51	85.72
F-8	120	71.53
F-9	62	96.64
F-10	30	81.65
F-11	27	94.11
F-12	20	98.78

**Figure 2 : Lafutidine tablet F- 12 Formulation****Figure 3 : Initially lafutidine tablet**



After 20 sec

Figure 4: Wetting time of F12 formulation

IN-VITRO DISINTEGRATION TIME :

Table 5 : Disintegration time of formulations F-1 to F-12

Tablet formulation	Disintegration time in sec.
F-1	65
F-2	50
F-3	30
F-4	76
F-5	45
F-6	32
F-7	50
F-8	40
F-9	25
F-10	25
F-11	20
F-12	18

Figure-5: In-vitro dissolution profile of F-1 to F-6 formulation

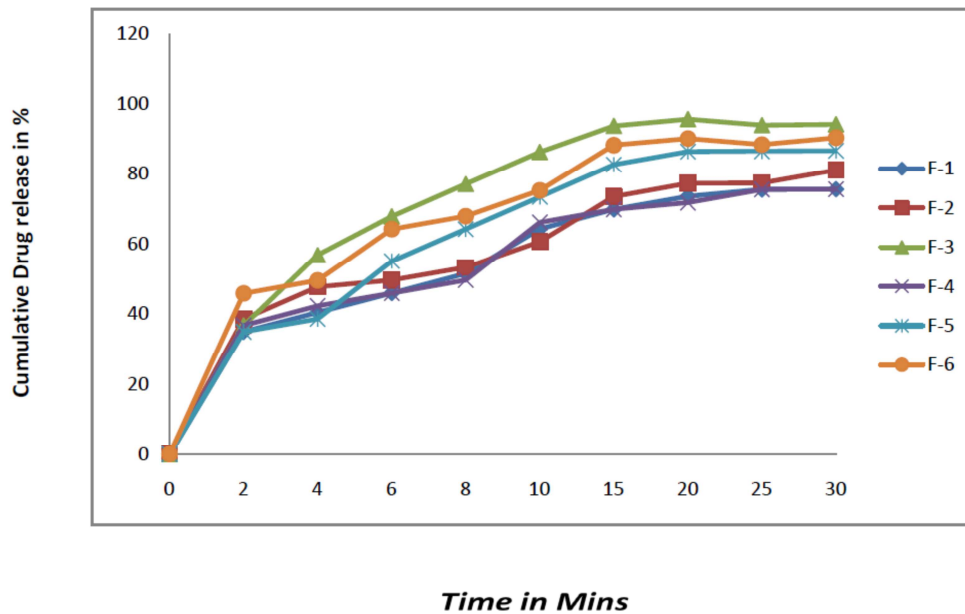
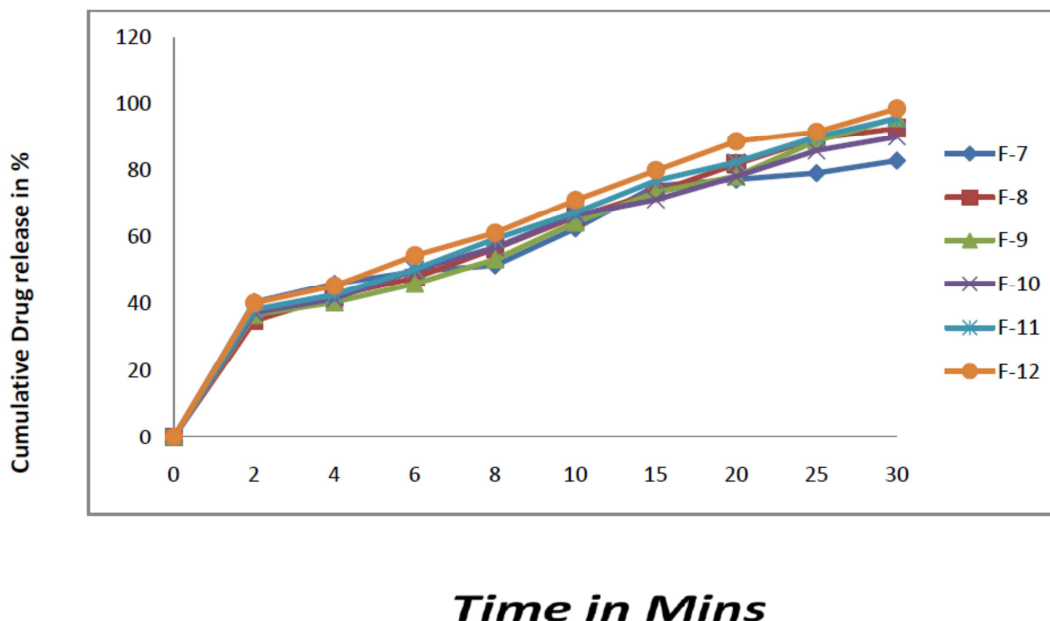


Figure-6: In-vitro dissolution profile of F-8 to F-12 formulation



REFERENCES

- [1] JJ Hirani; DA Rathod; KR. Vadalía. *Trop J Pharm Res*, **2009**,8,161-72.
- [2] Available from:URL: <http://en.wikipedia.org/wiki/Lafutidine>.
- [3] PM Young; RC Rowe; PJ Sheskey; ME Quinn. Handbook of Pharmaceutical Excipients; Published by Pharmaceutical Press and American Pharmacist Association, **2009**, 6th ed ; pp. 663-666
- [4] AH Kibbe; RC Rowe ; P.J Sheskey. Handbook of Pharmaceutical Excipients; Published by Pharmaceutical Press and American Pharmacist Association, **2009**, 6th ed ; pp.208-10.
- [5]RC Rowe; PJ Sheskey; PJ Weller . Handbook of pharmaceutical excipients. 4th ed. London: Pharmaceutical Press, **2003**.
- [6]SR Parakh; AV Gothoskar, **2003**,27,92-100.
- [7]BS Kuchekar; CB Atul; HS Mahajan. *Pharma Times*, **2003**,35,7-9.
- [8]Peptic Ulcer disease; Available from URL:<http://www.uptodate.com/contents/patient- information- pepticulcerdisease-beyond-the-basics>.